Papers

Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies)

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Abstract

Objective: To determine whether treatment with low dose aspirin and heparin leads to a higher rate of live births than that achieved with low dose aspirin alone in women with a history of recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies), lupus anticoagulant, and cardiolipin antibodies (or anticardiolipin antibodies).

Design: Randomised controlled trial.

Setting: Specialist clinic for recurrent miscarriages.

Subjects: 90 women (median age 33 (range 22-43)) with a history of recurrent miscarriage (median number 4 (range 3-15)) and persistently positive results for phospholipid antibodies.

Intervention: Either low dose aspirin (75 mg daily) or low dose aspirin and 5000 U of unfractionated heparin subcutaneously 12 hourly. All women started treatment with low dose aspirin when they had a positive urine pregnancy test. Women were randomly allocated an intervention when fetal heart activity was seen on ultrasonography. Treatment was stopped at the time of miscarriage or at 34 weeks' gestation.

Main outcome measures: Rate of live births with the two treatments.

Results: There was no significant difference in the two groups in age or the number and gestation of previous miscarriages. The rate of live births with low dose aspirin and heparin was 71% (32/45 pregnancies) and 42% (19/45 pregnancies) with low dose aspirin alone (odds ratio 3.37 (95% confidence interval 1.40 to 8.10)). More than 90% of miscarriages occurred in the first trimester. There was no difference in outcome between the two treatments in pregnancies that advanced beyond 13 weeks' gestation. Twelve of the 51 successful pregnancies (24%) were delivered before 37 weeks' gestation. Women randomly allocated aspirin and heparin had a median decrease in lumbar spine bone density of 5.4% (range −8.6% to 1.7%).

Conclusion: Treatment with aspirin and heparin leads to a significantly higher rate of live births in women with a history of recurrent miscarriage associated with phospholipid antibodies than that achieved with aspirin alone.

See editorial by Khamashta and Mackworth-Young

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Introduction

Phospholipid antibodies, lupus anticoagulant, and cardiolipin antibodies are associated with recurrent miscarriage, thrombosis, and thrombocytopenia.[1] Fifteen per cent of women with a history of recurrent miscarriage (three or more consecutive losses of pregnancy) have persistently positive results for phospholipid antibodies.[2] These women have a rate of fetal loss of 90% when no specific treatment is given during pregnancy.[3 4] Miscarriage has been attributed to thrombosis of the uteroplacental vasculature and placental infarction,[5 6] but the extent of placental disease cannot account for pregnancy loss in all cases.[6] Several treatments including corticosteroids,[7-10] low dose aspirin,[9 11] heparin,[8 11 12] and immunoglobulins[13] have been used either as single agents or in combination to try to improve the rate of live births in women with phospholipid antibodies. However, available data are limited by the small number of patients in individual studies, which also have had varying entry criteria and treatment protocols, and by the lack of standardisation of laboratory assays used to detect phospholipid antibodies. This last point has recently been addressed.[14-16]

The use of corticosteroids in pregnancy is associated with significant maternal and fetal morbidity.[8 9] Low dose aspirin or heparin are currently the favoured treatments. We determined whether the addition of low dose heparin to low dose aspirin results in a higher rate of live births than that achieved with low dose aspirin alone in women with a history of recurrent miscarriage associated with phospholipid antibodies.

Patients and methods

Local ethics committee approval was obtained and patients gave informed consent. Between April 1993 and July 1995, 90 patients were recruited from the recurrent miscarriage clinic at St Mary's Hospital in London.

Eligibility

Patients were eligible for this study if they had a history of three or more consecutive miscarriages and had positive results for phospholipid antibodies on at least two occasions more than eight weeks apart before becoming pregnant. Women with previous thromboembolism were excluded as they require thromboprophylaxis during pregnancy. Also excluded were those with systemic lupus erythematosus,[17] a uterine abnormality (detected on ultrasound scanning), hypersecretion of luteinising hormone,[18] and multiple pregnancy. Women were also excluded if either they or their partner had an abnormal karyotype.

Trial protocol

Women started taking low dose aspirin (75 mg daily) as soon as they had a positive pregnancy test (urinary human chorionic gonadotrophin concentration >50 IU/ml; Clearview, Unipath, Bedford). Vaginal ultrasound scans were performed from five weeks of amenorrhoea. When fetal heart activity was seen on ultrasonography women were randomly allocated either to continuing low dose aspirin or to self administered subcutaneous calcium heparin (5000 U 12 hourly; Calciparine, Sanofi Winthrop, Surrey) in addition to low dose aspirin. From 24 weeks' gestation pregnancies were monitored by serial ultrasonography and Doppler studies of the umbilical artery circulation. Treatment was stopped at the time of miscarriage or at 34 weeks' gestation.

Women randomly allocated heparin had dual energy *x* ray absorbitometry bone densitometry (Lunar Corporation, Madison, Wisconsin) of the lumbar spine (L2-L4) performed at 12 weeks' gestation and postnatally.

Laboratory assays

Sample collection and processing, which complied with national guidelines, was performed as previously described.[2 15]

Lupus anticoagulant—A coagulation screen consisting of the prothrombin time, activated partial thromboplastin time, and thrombin time was performed on all patients using an Organon Teknika XC Plus and standard methods. The activated partial thromboplastin time was also measured in test plasma samples diluted in the ratio of 80 to 20 parts with normal plasma. The dilute Russell's viper venom time was measured in duplicate on a semiautomated coagulometer (KC4; Heinrich Amelung, Lehbrinksweg, Lemgo) using a kit (Unicorn Diagnostics, London). Patient samples with a dilute Russell's viper time ratio of ≥ 1.1 (test:normal) were retested with a platelet neutralisation procedure consisting of washed, freeze-thawed platelets. A decrease of 10% or more in the ratio was considered to be positive for lupus anticoagulant.[15]

Anticardiolipin antibodies—Samples for IgG and IgM cardiolipin antibodies were assayed in duplicate using a standardised enzyme linked immunosorbent assay (ELISA).[16] Results were expressed in either GPL or MPLs. One such unit is defined as the binding activity of 1 μg/ml of affinity purified IgG or IgM standard.[19] A positive concentration of cardiolipin antibodies was considered to be IgG ≥ 5 GPL or IgM ≥ 3 MPL.[16]

Table 1 Demographic details and phospholipid antibody status of patients in trial

	Aspirin (n=45)	Aspirin and heparin (n=45)	P value
Median age (range) (years)	34 (22-44)	32 (23-40)	0.14
Median No (range) of previous miscarriages	4 (3-8)	4 (3-15)	0.57
No of patients with:			
First trimester miscarriages only	31	29	0.66*
First and second trimester miscarriages	13	13	1.0*
Second trimester miscarriages only	1	3	0.61*
Previous live birth	15	18	0.66*
No of patients positive for:			
Lupus anticoagulant only	34	40	0.17*
Cardiolipin IgG only	4	3	0.98*
Cardiolipin IgM only	1	0	
Lupus anticoagulant and cardiolipin	6	2	0.27

*Fisher's exact test; otherwise Mann-Whitney U test.

Randomisation

Patients were randomly assigned in equal proportion to the two treatment groups by means of a computer generated random number list (Systat 5.2.1; Macintosh). The randomisation list was kept by an independent member of staff not involved in the trial. All patients remained in their originally allocated treatment group and the outcome of all pregnancies was analysed.

Sample size

Data available at the start of the study showed that the rate of live births among women treated with low dose aspirin alone is 30%.[10] We considered that an improvement to 60% with the addition of heparin would be clinically important. A power calculation at the start of the study indicated that between 80 and 90 women would have to be recruited to achieve a study power of 80% at a significance level of 0.05 (two tailed) to prove the hypothesis correct: that the use of low dose aspirin and heparin leads to a higher rate of live births than that achieved with low dose aspirin alone.

Statistical analysis

The primary outcome measure of this trial—live birth or miscarriage—was compared between the two groups using Fisher's exact test. Secondary quantitative outcome comparisons were made using the Mann-Whitney U test.

Results

Forty five women were randomly allocated low dose aspirin alone and 45 low dose aspirin and heparin. Table 1 shows their demographic details and phospholipid antibody status. The median concentration of IgG cardiolipin antibodies was 12.5 GPL (range 5.2-80 GPL). One woman with positive results for IgM cardiolipin antibodies had a concentration of 15 MPL. No woman withdrew from the trial.

The outcome of the 90 pregnancies is shown in figure 1 and table 2. Treatment with low dose aspirin in combination with heparin led to a significantly higher rate of live births (71%) than that achieved with low dose aspirin alone (42%; odds ratio 3.37 (95%

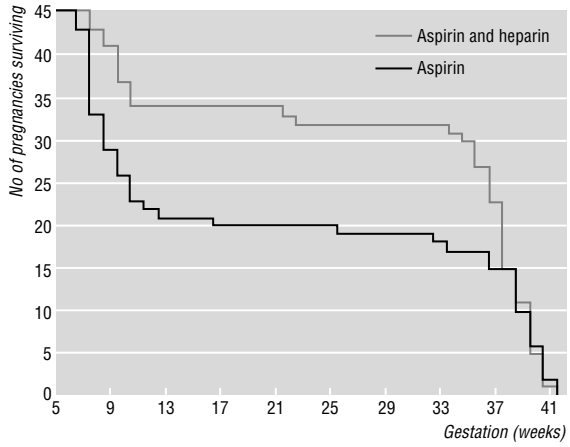

Fig 1 Outcome of pregnancy in women with recurrent miscarriages and phospholipid antibodies who were given aspirin or aspirin and heparin. All pregnancies of longer than 32 weeks' gestation resulted in live birth

Table 2 Details of pregnancies of patients in trial

	Aspirin (n=45)	Aspirin and heparin (n=45)	P value
Median gestation (range) at randomisation (weeks)	6.6 (5.1-8.3)	6.7 (5.0-8.0)	0.32*
No of live births	19	32	0.01†
No of miscarriages	26	13	

*Mann-Whitney U test.
†Fisher's exact test.

confidence interval 1.40 to 8.10)). The birth weights and gestation at delivery were similar in the two groups (table 3).

Twelve of the 51 women with successful pregnancies (24%) delivered prematurely (<37 weeks' gestation). This was due to preterm labour in two out of 19 women treated with low dose aspirin (11%) and in five out of 32 women treated with low dose aspirin and heparin (16%; P=0.70). Intrauterine growth retardation (estimated fetal weight below the 10th centile for gestational age) was the indication for delivery in one woman treated with low dose aspirin (5%) and for three women treated with low dose aspirin and heparin (9%; P=0.99). One woman treated with low dose aspirin alone was delivered at 36 weeks' gestation for pre-eclampsia. No woman developed a thromboembolic complication during pregnancy or the puerperium.

Most miscarriages in the two groups occurred in the first trimester (table 4). In pregnancies that progressed beyond 13 weeks' gestation there was no difference in the outcome of those treated with low dose aspirin alone compared with those treated with low dose aspirin and heparin.

All babies were examined by a paediatrician shortly after delivery. No congenital abnormalities were detected. Three babies were admitted to the neonatal unit because of prematurity. Only one baby, who was delivered by caesarean section at 32 weeks' gestation for intrauterine growth retardation to a mother treated with low dose aspirin alone, required ventilatory support for a week. The two other babies, delivered at 33 and 36 weeks' gestation, were admitted to the neonatal unit for help with feeding. One baby had a parietal lobe infarction two days after delivery (diagnosed on magnetic resonance imaging). This baby was born at 42 weeks' gestation to a mother who was treated with low dose aspirin alone. The mother had high concentrations of IgG cardiolipin antibodies (median 80 GPL) and was negative for lupus anticoagulant. The baby tested negative for both IgG and IgM cardiolipin antibodies.

Table 3 Details of pregnancies resulting in live birth

	Aspirin (n=19)	Aspirin and heparin (n=32)	P value
Median (range) gestation (weeks):			
At randomisation	6.7 (5.6-8.3)	6.8 (5.0-8.0)	0.58
At delivery	39.6 (32.4-41.7)	38.0 (33.9-41.4)	0.53
No of deliveries before 37 weeks' gestation	4	8	0.35*
Median birth weight (range) (g)	3080 (1300-4350)	3330 (1510-4140)	0.07
Male:female	7:12	19:13	0.15*

*Fisher's exact test; otherwise Mann-Whitney U test.

Both low dose aspirin and heparin were well tolerated. Of those taking heparin, none developed thrombocytopenia or had symptomatic complications apart from mild bruising localised to the injection site. These women had a median decrease in lumbar spine bone density of 5.4% (range −8.6% to 1.7%) between 12 weeks' gestation and postnatally (median 8 weeks; range 0-12). No woman had a vertebral fracture.

Discussion

This trial has shown that treatment with aspirin and low dose heparin leads to a significantly higher rate of live births than that achieved with aspirin alone in pregnant women with a history of recurrent miscarriage associated with phospholipid antibodies.

The laboratory assays used to detect phospholipid antibodies in this study complied with recently issued international guidelines for the testing of lupus anticoagulant and cardiolipin antibodies.[14-16] The phospholipid antibody status of the patients recruited to this study was similar to that in a prevalence survey of 500 consecutive women with recurrent miscarriage in that most patients were positive for lupus anticoagulant alone and there was little crossover between lupus anticoagulant and cardiolipin antibodies positivity.[2]

Trial design

The trial was not blinded as it was not considered ethical to ask a pregnant woman to self administer twice daily subcutaneous injections of a placebo for 28 weeks. The most common type of miscarriage in women with phospholipid antibodies occurs in the first trimester after fetal heart activity has become established.[3,4] Entry into the trial and randomisation therefore occurred only when fetal heart activity was

Table 4 Details of unsuccessful pregnancies

	Aspirin (n=26)	Aspirin and heparin (n=13)	P value
Median (range) gestation (weeks):			
At randomisation	6.5 (5.1-8.3)	6.4 (5.2-7.4)	0.83
At miscarriage	8.3 (7.0-25.7)	9.4 (7.3-23.6)	0.20
No with loss of pregnancy:			
Under 14 weeks	24	11	0.59*
Between 14 and 28 weeks	2	2	0.62*

*Fisher's exact test; otherwise Mann-Whitney U test.

seen on ultrasonography. Treatment was stopped at 34 weeks' gestation to minimise the duration of exposure to both aspirin and heparin. All women in the trial attended for supportive care, in the form of weekly ultrasound scans and psychological support, during the first trimester. This has been reported to have a significant beneficial effect on pregnancy outcome in women with a history of recurrent miscarriage.[20]

Phospholipid antibodies and miscarriage

Studies on human tissue and in mice suggest that phospholipid antibodies cause pregnancy loss by binding to phospholipids expressed on the invading trophoblast,[21 22] thereby inhibiting successful embryonic implantation into the endometrium. Once placentation is established their thrombogenic action leads to decreased placental perfusion and subsequent infarction.[5 6] We recently reported that non-pregnant women with a history of recurrent miscarriage in association with phospholipid antibodies are in a prothrombotic state.[23] This thrombogenic potential may be exacerbated by the known hypercoagulability that occurs in pregnancy.

Low dose aspirin may improve pregnancy outcome in women with phospholipid antibodies by irreversibly blocking the action of cyclo-oxygenase in platelets, thereby inhibiting platelet thromboxane synthesis and preventing thrombosis of the placental vasculature.[24] Heparin may act to reduce fetal loss by binding to phospholipid antibodies, thereby protecting the trophoblast phospholipids from attack[25] and promoting successful implantation in early pregnancy, in addition to its anticoagulant action. This is supported by the finding that there was no difference in pregnancy outcome between the two treatment arms in the pregnancies that survived beyond 13 weeks' gestation. By this time the first wave of trophoblast invasion is complete and placentation established.

High complication rate despite treatment

One quarter of successful pregnancies were delivered prematurely. This confirms previous reports of a high incidence of pregnancy complications in women with phospholipid antibodies[3-6] and emphasises the need for close antenatal surveillance. The finding that most miscarriages (>90%) occurred before 14 weeks' gestation confirms previous prospective observations in women with phospholipid antibodies who received no pharmacological treatment during pregnancy and who were followed up from the time that they had a positive pregnancy test.[4] Babies born to mothers treated with low dose aspirin and heparin tended to be of greater weight than those born to mothers treated with low dose aspirin alone, but this may be confounded by the higher proportion of boys born to mothers given aspirin and heparin (table 3).

As the long term use of heparin is associated with the development of osteopenia, bone density measurements were performed on women randomly allocated heparin. The median loss in lumbar spine bone density of 5.4% is equivalent to that lost after six months of lactation.[26] Osteopenia associated with heparin is reversible when heparin treatment is stopped.[27]

In conclusion, the poor obstetric outlook for women with a history of recurrent miscarriage in association with phospholipid antibodies may be improved with low dose aspirin, but it is further and significantly improved with the combined use of low dose aspirin and low dose heparin. This combination may promote successful embryonic implantation in the early stages of pregnancy and protect against thrombosis of the uteroplacental vasculature after successful placentation. Future studies should be aimed at refining the protocol used in this trial to determine the benefits of preconceptual administration of heparin and whether it can be stopped after 13 weeks' gestation without adversely affecting the rate of live births.

Key messages

- The prognosis for pregnancies in women with recurrent miscarriage associated with phospholipid antibodies is poor
- This randomised controlled trial found that the prognosis improved with low dose aspirin and was further improved with the addition of low dose heparin to the aspirin
- This combination may promote successful embryonic implantation in the early stages of pregnancy and protect against thrombosis of the uteroplacental vasculature after successful placentation
- Most miscarriages occurred before 13 weeks' gestation
- Nearly a quarter of the successful pregnancies were delivered prematurely (before 37 weeks' gestation), so close surveillance is necessary
- Long term use of low dose heparin was associated with few complications

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Variations in use of cardiology services in a health authority: comparison of coronary artery revascularisation rates with prevalence of angina and coronary mortality

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Abstract

Objective: To explore the relation between rates of coronary artery revascularisation and prevalence of angina to assess whether use of health services reflects need.
Design: Prevalence of angina symptoms determined by postal questionnaire on 16 750 subjects (18 to 94 years). Comparison of data on use of coronary artery revascularisation with prevalence of symptoms and mortality from coronary heart disease.
Setting: Health authority with population of 530 000.
Subjects: Patients admitted to hospital for coronary heart disease; patients who died; and patients undergoing angiography, angioplasty, or coronary artery bypass graft. Cohort of 491 people with symptoms from survey.
Main outcome measures: Pearson's product moment correlation coefficients for relation between variables.
Results: Overall, 4.0% (95% confidence interval 3.7% to 4.4%) of subjects had symptoms. Prevalences varied widely between electoral wards and were positively associated with Townsend score ($r=0.79$; $P<0.001$), as was mortality, but the correlation between admission rates and Townsend score was less clear ($r=0.47$; $P<0.01$). Revascularisation rate and Townsend score were not associated. The ratio of revascularisation to number experiencing symptoms was inversely related to Townsend score ($r=-0.67$; $P<0.001$). The most deprived wards had only about half the number of revascularisations per head of population with angina than did the more affluent wards. In affluent wards 11% (13/116) of those with symptoms had coronary angiograms compared with only 4% (9/216) in poorer wards ($\chi^2=4.96$; $P=0.026$). Townsend score also inversely correlated with revascularisations per premature death from coronary heart disease ($r=-0.55$; $P<0.01$) and revascularisations per admission for myocardial infarction ($r=-0.47$; $P<0.01$).
Conclusion: The use of interventional cardiology services is not commensurate with need, thus exhibiting the inverse care law.

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Introduction

Tudor Hart enunciated the sad fact that "the availability of good medical care tends to vary inversely with the need for it in the population served"; often summarised as the inverse care law.[1] More recent work has suggested health authorities should carry out "equity audits" to determine whether healthcare resources are being utilised in accordance with need.[2]

In the treatment of angina, increased availability of coronary artery revascularisation, such as coronary artery bypass graft and angioplasty, has been recommended.[3] There is, however, distinct national and local variation in rates of treatment.[4,5] While some have shown poor access to services among residents of deprived areas[6] others have found no such relation.[7]

In general, utilisation of revascularisation treatment for angina will be influenced by the following: firstly, need—epidemiology of disease that, even after differences in age and structure are considered, varies substantially from place to place, at both national and

local levels[8]; secondly, supply—the availability of cardiologists and centres carrying out revascularisation procedures has been shown to be a substantially important predictor of utilisation[4 9]; thirdly, demand—in turn affected by patients' consultation thresholds, general practitioners' referral thresholds, and cardiologists' referral and intervention thresholds.

We examined the prevalence of symptoms of angina at small area level within a city, Sheffield, no part of which is more than 20 km from a major cardiological centre.

Methods

Sheffield has a population of 530 000, living in both rural and urban areas. It has 29 electoral wards ranging in size from 12 400 to 31 800 residents. Specialist cardiological investigation and treatment is carried out at the Northern General Hospital, which is located closest to some of the wards with the highest standardised mortality ratios for coronary heart disease. This hospital also provides specialist cardiological services to the surrounding districts in South Yorkshire and North Derbyshire, thus serving a population of around 1.5 million.

Determining prevalence of angina

After we obtained ethical approval we used the health authority's population register to generate a random sample, stratified for age and sex, of residents registered with general practitioners. The stratification was by six age and sex bands: men or women and ages 18-34, 35-54, and 55-94 years. A postal questionnaire to determine the prevalence of a range of common symptoms was sent to this sample of 16 750 residents in March 1994.

The sample was also stratified at the electoral ward level, such that the prevalence of the various conditions studied could be estimated with reasonable confidence limits for each of the 29 electoral wards.

We used a slightly simplified form of the World Health Organisation (Rose) angina questionnaire[10] to assess the prevalence of angina symptoms (D Cook, personal communication). To improve the specificity only those with more severe symptoms were included. Up to two reminders (one full questionnaire and one postcard) were sent to those who failed to respond. By preserving a unique patient number we directly linked questionnaire data from individual respondents with health event data such as hospital admissions and procedures.

Health event and census data

The health authority's database was used to examine hospital admission activity at electoral ward level—all these data were based on hospital admissions not consultant episodes, which can be multiple within a single admission. We calculated overall admission rates (emergency and elective) for coronary heart disease (ICD-9 (international classification of diseases, ninth revision) codes 410-414), myocardial infarction (code 410), coronary artery bypass graft (codes K40-K47 in the fourth revision of Office of Population Censuses and Surveys classification of operations[11]), and angioplasty (codes K49-K50.1). At individual level, particular attention was paid to admissions for angiography (codes K63-K65), coronary artery bypass graft, and angioplasty from 1 April 1991 to 31 December 1995, the time period just before and after the survey. For survey respondents, linked activity data were examined at the individual patient level, thus multiple admissions of the same patient were counted only once.

We used the 1991 census to calculate the Townsend score[12] for each electoral ward. This score is designed to be high in areas of increased deprivation.

Table 1 Prevalence of symptoms of angina[10] by sex and age band

Sex and age (years)	No (%) of patients
Men:	
18-34	32/1711 (1.9)
35-54	45/1758 (2.6)
55-94	172/1975 (8.7)
18-94	249/5444 (4.6)
Women:	
18-34	22/2027 (1.1)
35-54	48/2079 (2.3)
55-94	172/2689 (6.4)
18-94	242/6795 (3.6)

Data handling and analysis

Survey data were analysed with EpiInfo.[13] When appropriate we standardised individual ward data directly by using the England and Wales population as the reference. Data were plotted as scatter plots, and Pearson's product moment correlation coefficients were calculated.

Results

Of the 16 750 questionnaires sent out, 12 240 (73%) were completed and returned. After we excluded a further 1160 that were returned without reaching the person for whom they were intended, the response rate was 79%. Table 1 shows the prevalence of symptoms of angina by age and sex for Sheffield as a whole.

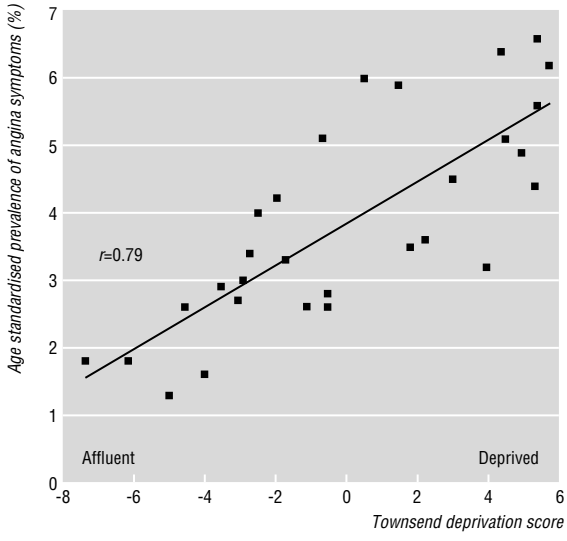

Fig 1 Prevalence of angina symptoms compared with Townsend deprivation score

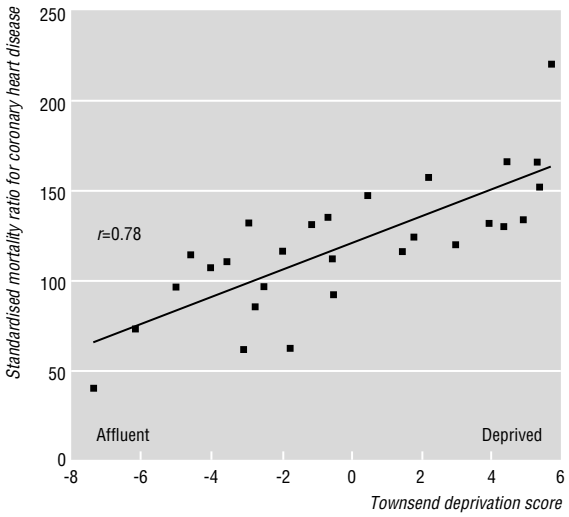

Fig 2 Mortality from coronary heart disease (standardised mortality ratio 1988-92 for ages 35-64) compared with Townsend deprivation score

Overall, 4.0% (95% confidence interval 3.7% to 4.4%) experienced symptoms of pain or discomfort in the chest when walking at an ordinary pace on the level. The proportion was 4.6% (4.0% to 5.2%) in men compared with 3.6% (3.2% to 4.0%) in women and was substantially higher in older age groups.

Prevalence of symptoms and mortality from coronary heart disease compared with deprivation

There was wide variation in the age standardised prevalence of symptoms of angina between electoral wards; it ranged from under 2% in some to over 6% in others. Figure 1 shows that there was a strong positive relation ($r=0.79$; $P<0.001$) between the Townsend score of the electoral ward and the prevalence of symptoms.

Figure 2 shows a similar relation when we plotted premature mortality (<65 years) from coronary heart disease against Townsend score. Again, there was wide variation in the mortality between electoral wards, and mortality was strongly and significantly correlated with Townsend score ($r=0.78$; $P<0.001$).

Unlike symptoms of angina or mortality from coronary heart disease, admission rates for coronary heart disease varied only twofold between the highest and lowest electoral wards. There was still a significant correlation between admission rates and Townsend score ($r=0.47$; $P<0.01$), but it was now smaller than for prevalence of angina symptoms or mortality from coronary heart disease. There was, however, no relation at all between the rates of coronary artery revascularisation (angioplasty and coronary artery bypass graft) and Townsend score.

To determine whether utilisation of coronary artery revascularisation was uniformly related to need we calculated the ratio of revascularisations to the number in the electoral ward estimated to have symptoms of angina. Figure 3 shows this index plotted against Townsend score. There was a clear variation between electoral wards in these ratios: deprived wards had only about half the numbers of revascularisations per head of population estimated to have angina symptoms than did affluent wards ($r=-0.67$; $P<0.001$).

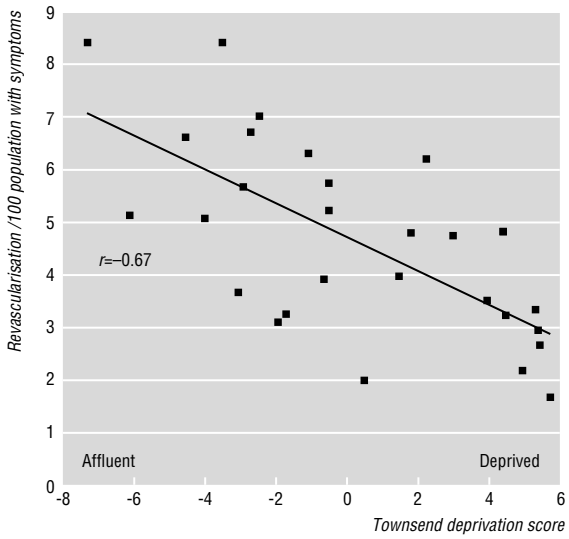

Fig 3 Coronary artery revascularisations per number with symptoms of angina compared with Townsend deprivation score

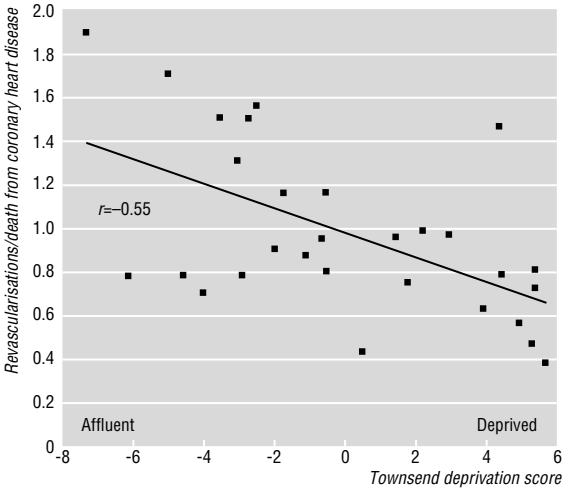

Fig 4 Coronary artery revascularisations per death from coronary artery disease compared with Townsend deprivation score

Proxy measures of prevalence of angina

As health symptom surveys may overestimate the true prevalence of angina, two proxy measures were compared with the coronary artery revascularisation rate. Figure 4 shows a similar inverse relation between revascularisations per premature death (<65 years) from coronary heart disease and Townsend score ($r=-0.55$; $P<0.01$). Figure 5 shows that the same was true when revascularisations per myocardial infarction were compared with Townsend score ($r=-0.47$; $P<0.01$).

Linkage data for survey and service utilisation

It may not be valid to assume that relations found at small area level exist at the level of the individuals who make up those areas (the "ecological fallacy"). We also

Table 2 Proportions of subjects who reported symptoms of angina and had undergone angiography

Wards	No of subjects	Proportion (%) (95% confidence interval)
Ten most affluent	13/116	11.2 (5.5 to 16.9)
Ten most deprived	9/216	4.2 (1.5 to 6.9)

considered, therefore, data at both small area and individual level.

Individual survey results from respondents who had angina symptoms were linked to health event data to determine whether they had been admitted to hospital for angiography in the three years before and 21 months after the survey. Validation showed 100% linkage accuracy—that is, no relevant records were lost in this process. The angiography rate was found to be 20 times higher in those with angina identified through the survey (19.7/1000 population) compared with the rate in the general population (1.0/1000 population). Table 2, however, shows that there was substantial difference between more affluent and less affluent electoral wards: in the 10 most affluent wards 11.2% (13/116; 95% confidence interval 5.5% to 16.9%) had had angiography compared with 4.2% (9/216; 1.5% to 6.9%) in the 10 most deprived electoral wards ($\chi^2 = 4.96$; $P = 0.026$). Finally, 6.9% (22/321) of those aged under 70 years with angina symptoms had had an angiogram compared with only 1.2% (2/170) of those aged 70 and over ($\chi^2 = 6.53$; $P = 0.01$).

Discussion

Our results show a large local variation in both mortality from coronary heart disease and prevalence of angina as determined by a population survey. Both mortality and prevalence of symptoms were strongly correlated with material deprivation, as estimated by the Townsend score, at electoral ward level. We found that the ratio of rates of coronary artery revascularisation to the prevalence of angina symptom varied substantially across the city and was inversely proportional to deprivation. Thus, use of services was not commensurate with need and seemed to exhibit the inverse care law,[1] even though the availability of care is the same.

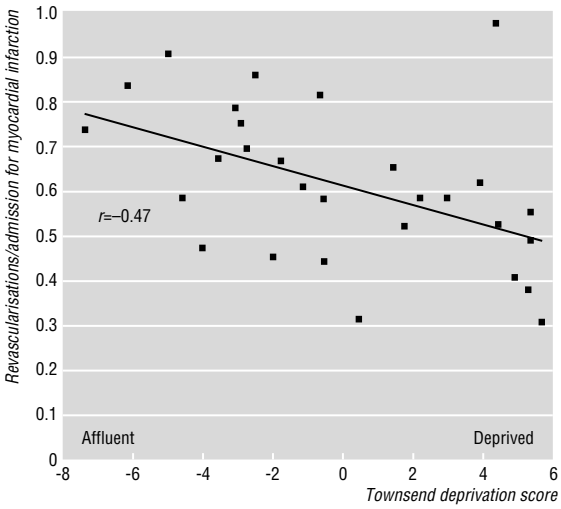

Fig 5 Coronary artery revascularisations per admission for myocardial infarction compared with Townsend deprivation score

The data on rates of coronary artery revascularisation refer only to procedures undertaken within the NHS, and private sector activity may add another 10-20% to this.[14] Given that private sector activity is likely to be higher for more affluent wards, however, and indeed that private insurance coverage in professional groups is much higher than in unskilled manual groups (23% compared with 2%[15]) the differences in use in relation to need for these services between the affluent and deprived populations may be even greater than described.

Response rates to the electoral ward survey varied between 63% and 88%, with affluent wards tending to have highest response, and this might have influenced the results. All but five of the 29 wards, however, had a response rate of over 70%. Moreover, the lower response rates in deprived electoral wards are only of concern if they result in deprived respondents being less representative of the deprived population than affluent respondents are of the affluent population; there is no evidence that such response bias exists.

Problems have been identified regarding the utility of the angina questionnaire,[10] particularly regarding its specificity in women.[16 17] The health survey for England,[18] which used similar questionnaire and survey methodology, gave an overall prevalence of 3.1% (95% confidence interval 2.7% to 3.6%) in an equivalent age group. Even in their 18-34 year group the estimated prevalence was about 1%. The same survey, by using diagnosis as reported by patients, produced estimates of 4.3% in men and 3.4% in women; broadly similar to our results. Other estimates are lower at 1.6% in men and 1.2% in women, but these are derived only from numbers of patients consulting general practitioners in a single year.[19] Although these methodological problems may have implications for the absolute values of symptoms of angina, however, there is no evidence that specificity and sensitivity rates are likely to vary according to level of deprivation, so any impact on the comparison between affluent and deprived populations is probably insignificant. Prevalence of other symptoms (for example, hip pain) examined in our survey and elsewhere[20] showed little or no relation to deprivation, thus failing to support the notion that people in lower socioeconomic groups complain more about symptoms. Moreover, the relation shown between mortality from coronary heart disease and deprivation strongly reinforces our finding with respect to the distribution of angina symptoms.

The hospital data on admissions, like other routine data, have limitations,[21] but the data used for this study have been subject to local validation between provider and purchaser and suffer from these problems much less than most hospital episode statistics datasets.

Patients who smoke are known to have poorer results after revascularisation procedures,[22-24] and though this has led to considerable debate, many clinicians are reluctant to perform these procedures unless patients have stopped smoking.[25] One possible explanation for the findings reported here is that they are related to the prevalence of smoking, which is higher among less affluent groups. If we assumed that prevalence of smoking among angina sufferers is twice as high in the more deprived parts of Sheffield,

however, this would explain only half of the observed difference in the difference of the revascularisation to prevalence ratio between electoral wards. To illustrate, the angiography rate in those with angina identified through the survey was found to be 11% (13/116) in the 10 most affluent wards and 4% (9/216) in the 10 most deprived wards. National and local data suggest that about 83% of affluent populations are likely to be non-smokers but only 65% of deprived populations.[26 27] Even if the smokers had been excluded from treatment (that is, from the numerator) and if the denominator was adjusted to reflect the likely number of non-smokers, the angiography rate in affluent wards would still be twice that in deprived wards—that is, 13% ($13/(116\times0.83)$) *v* 6% ($9/(216\times0.65)$), respectively. In future studies, however, smoking prevalence and measures of comorbidity from hospital activity datasets could be controlled for directly. This would also be important in the investigation of our finding of differential revascularisation rates between older and younger patients as age alone should not be a determining factor in selection of patients for this treatment. Selection of elderly patients for angiography is more complex than for younger patients, but it has been argued that symptomatic benefit is similar for younger and older patients and that earlier referral and investigation might yield a population with lower operative risk.[28]

Recommendations for action

We recommend an audit of referral of angina patients, particularly seeking to redress this apparent inequity. If consultation thresholds are higher in the less affluent areas it should be determined whether education of patients is required to encourage consultation by those with symptoms suggestive of angina. General practitioners should be aware of referral recommendations and potential benefits of treatment for those with angina. Detailed discussion of these results with cardiologists suggests that once patients have been referred for angiography those needing revascularisation are prioritised only on the basis of the severity of their disease. Finally, if cardiology services are expanded, steps should be taken to ensure that those in less affluent parts of the city receive a fairer share of these health services.

We thank Dr Gordon Reid for advice during the planning of the morbidity survey.

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Conflict of interest: None.

Key messages

- There is a large local variation in mortality from coronary heart disease and in the prevalence of angina symptoms and both of these are strongly correlated with material deprivation
- Morbidity, as prevalence of angina symptoms, shows the same relation as mortality
- The use of coronary artery revascularisation services is not commensurate with need and exhibits the inverse care law even though the supply of care is the same
- Further work is required to ensure that the use of and access to facilities ensures that health care is targeted where it will have the greatest effect

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Relation between bed use, social deprivation, and overall bed availability in acute adult psychiatric units, and alternative residential options: a cross sectional survey, one day census data, and staff interviews

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Abstract

Objectives: To examine the relation between bed use, social deprivation, and overall bed availability in acute adult psychiatric units and to explore the range of alternative residential options.
Design: Cross sectional survey, combined with one day census data; ratings by and interviews with staff; examination of routine data sources.
Settings: Nationally representative sample of acute psychiatric units.
Subjects: 2236 patients who were inpatients on census day.
Main outcome measures: Bed occupancy levels, judged need for continuing inpatient care, reasons preventing discharge, scores on the Health of the Nation outcome scales.
Results: Bed occupancy was related to social deprivation and total availability of acute beds ($r = 0.66$, 95% confidence interval 0.19 to 0.88, $F = 8.72$, $df = 2, 23$; $P = 0.002$). However, 27% (603/2215) of current inpatients (61% (90/148) of those with stays of >6 months) were judged not to need continuing admission. The major reasons preventing discharge were lack of suitable accommodation (37% (176/482) of patients in hospital <6 months *v* 36% (31/86) of those in hospital >6 months); inadequate domiciliary based community support (23% (113) *v* 9% (8)); and lack of long term rehabilitation places (21% (100) *v* 47% (40)). Scores on the Health of the Nation outcome scale were generally consistent with these staff judgments.
Conclusions: The shortage of beds in acute psychiatric units is related to both social deprivation and the overall availability of acute beds. Patients currently inappropriately placed on acute admission wards should be relocated into more suitable accommodation, either in hospital or in the community. A range of provisions is required; simply providing more acute beds is not the answer.

Introduction

The policy to establish more community based mental health services is now well established.[1] Both professional and public concern remains, however, that inadequate resources may have been allocated to carrying out the policy and that the reduction of beds in the old mental hospitals has proceeded much more rapidly than the expansion of new hospital and community services to replace them. Acute psychiatric units, especially those in inner cities with high levels of surrounding social deprivation, have been described as "in crisis,"[2] with no available beds, an accumulation of difficult and disturbed patients, increased rates of extracontractual referrals, and apparently unsolvable problems of over-occupancy.[3] This has led to calls for more acute beds[4,5] and an end to hospital closures.[6] It has also provided the impetus for a recent ministerial announcement about the importance of a "spectrum of care" that does not neglect the need for "24 hour nursed" beds to deal with some of the most difficult patients who need longer term residential care.[7] The NHS Executive's guidance suggests a need for relatively small (12 bed) units, provided at an average level of 10 per 100 000, at an estimated overall running cost of £35 000-£50 000 per resident per year depending on size and location.

Despite passionate debate, the evidence on bed use in acute psychiatric units is sparse and is based on either small samples of districts[8,9] or studies of conditions in inner London alone.[2,3] It is therefore important to examine these problems in a national context and to explore the relation between bed use, indices of social deprivation, and overall availability of beds. We aimed to investigate why people are remaining in hospital and what alternative accommodation might meet their needs.

Methods

Sampling

We drew up a list from the 1991 census of all district health authorities in England and Wales as of April 1994, together with their corresponding Jarman underprivileged area 8 scores[10] as the principle stratifying variable. This resulted in a sampling frame of 119 authorities. We then ranked these into six "bands" (five containing 20 districts and one containing 19) and randomly selected seven districts from each band (42 in total). We obtained from each district information on the number of providers of acute psychiatric inpatient services. If there was only one provider (a trust) this was selected into the sample. Where there were multiple providers, one was selected randomly. In cases of refusal or non-response, a new district was randomly selected from the same band.

Procedure

Recruitment of services took place between April and July 1995 and data collection between May and October 1995. Contact was established with each provider, initially through the chief executives, and researchers visited the units to train staff to use the data collection instruments. Because of the necessity to phase sites into the project, a single census day common to all participating districts was impractical, so sites chose their own census day. A locally appointed liaison officer supervised data collection on each site. A researcher was available on the census day to help.

Health of the Nation outcome scales

- Overactive, aggressive, disruptive behaviour
- Non-accidental self injury
- Alcohol or drug misuse
- Cognitive problems
- Physical illness or disability problems
- Problems associated with hallucinations and delusions
- Problems with depressed mood
- Other mental or behavioural problems
- Problems with relationships
- Problems with activities of daily living
- Problems with living conditions
- Problems with occupation and activities

For all scales 0 = no problem; 1 = minor problem, requiring no action; 2 = mild problem but definitely present; 3 = moderately severe problem; 4 = severe to very severe problem. Total severity score is sum of all rated scales

Instruments

Data were collected with a specially designed form to record basic information about numbers of available beds, staffing levels, and acute unit activity. Information was also collected on the range of locally based community services, such as community mental health teams, crisis services, and supported housing. A census day was selected for the acute wards in each provider, and senior nursing staff were asked to collect the information on all patients recorded as occupying a bed on that day in consultation with the named nurse responsible for that individual patient's care. This included patients on leave, absent without leave, and temporary transfers to secure facilities or non-psychiatric beds. Patients in specially designated beds for elderly functionally ill people, in mother and baby units, and in secure units were excluded. Staff completed a background data sheet covering age, sex, primary diagnosis, ethnic group, Mental Health Act status, and date of admission. They also completed the 12 item field trial version of the Health of the Nation outcome scales,[11] which contains 11 items, each rated 0-4, covering common symptoms and functional problems (box).

Finally, members of staff were asked to indicate whether they judged that the individual should remain on an acute inpatient ward and to complete a standardised checklist of the reasons preventing discharge or transfer to a more appropriate setting.[12]

Analysis

Means, standard deviations, and confidence intervals are quoted as appropriate. When the data are skewed, medians and ranges are given. A priori hypotheses were tested with two tailed tests on frequency tables and means. For categorical data, differences were analysed with χ^2 tests. For continuous data, when approximately normally distributed, means were compared with *t* tests and one way analysis of variance. Otherwise, Mann-Whitney U tests were used. Bivariate correlations and regression analyses were used to investigate the relation between continuous variables. Linear trends for ordinal data were investigated with χ^2 for trends. All analyses were performed with the statistical software SPSS version 6.1.

Results

The sample

A sample of 38 providers (all but one having trust status) was achieved out of the original aim of 42. Three of the missing districts did not reply to repeated requests to supply data, and one withdrew for "internal reasons." The participating services covered total catchment area populations of 11.1 million (10.4 million in England and 730 000 in Wales). This represents 22% and 26% of the total population of England and Wales respectively. The median population size served by the providers was 236 000 (range 95 000-857 000).

In all, 34 out of 38 of the services (89%) returned usable census data. The Jarman scores and geographical location (urban, rural, or mixed) of the 34 services that provided data were compared with the eight that did not, and there was no evidence to suggest a difference in Jarman scores (Mann-Whitney U = 132, P = 0.91). When services were compared by geographical location, there was insufficient data to perform statistical analyses, but there was evidence of an underrepresentation of mixed locations in the eight services not returning data. Representation of urban and rural settings was similar.

Information was provided on 2236 patients. Of these, 48.2% (1074) of patients were resident in acute units on general hospital sites, and 45.1% (1009) were resident in acute units on mental hospital sites; the remaining 6.7% (149) of patients were accommodated in acute wards in other locations. In all, 52.0% (1139/2129) of the census patients were female, the mean age was 41 (SD = 15.07) years, 88.0% (1950/2217) of patients were white, and 69.9% (1562/2234) were "informal" (that is, voluntary patients not detained under a section of the Mental Health Act). Altogether, 74.5% (1652/2216) of patients had schizophrenia or mood disorder, and substance misuse, neurosis, and personality disorder accounted for 6.5% (143), 6.2% (130), and 6.2% (138) respectively. The median length of stay was 28.5 days (lower quartile, 11 days; upper quartile, 69 days). This kind of cross sectional sample is biased towards those with longer current stays; 6.7% (149/2208) of patients in the sample had current lengths of stay greater than six months and can therefore be regarded as "new" long stay patients.[13] The prevalence of these patients in general hospital based acute units was almost double the prevalence in mental hospitals (9.3% (67/724) *v* 4.8% (25/516)).

Altogether, 28 services returned information on community services, of whom 21 reported having multidisciplinary community mental health teams. However, only three services provided a crisis team (defined as providing evening and weekend cover; taking referrals mainly from secondary or tertiary services; and used as an alternative to admission to hospital). Seventeen of the 25 services without specialist crisis teams relied on an on call system whereby medical staff could be accessed through the local accident and emergency department. Eight services provided an "extended hours" service, but not 24 hours—for example, a community psychiatric nurse on call 9 am to 5 pm seven days a week or a rota of community mental health team workers. Four services provided an out of hours helpline for clients known to the

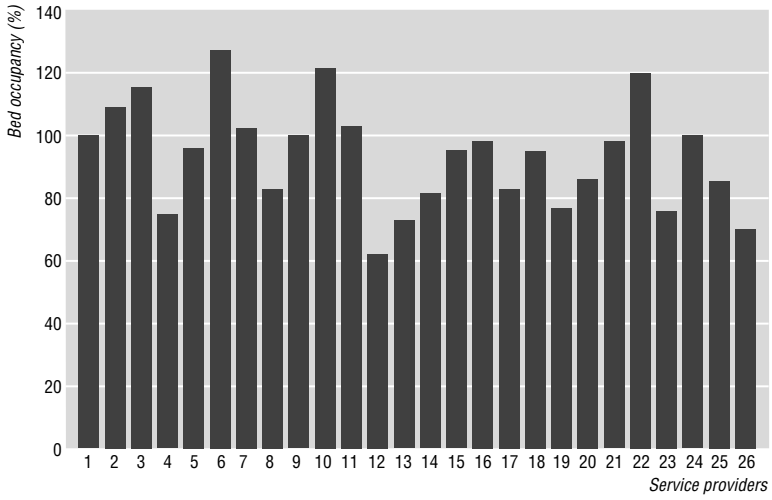

Fig 1 Distribution of percentage bed occupancy ranked by Jarman underprivileged area 8 score

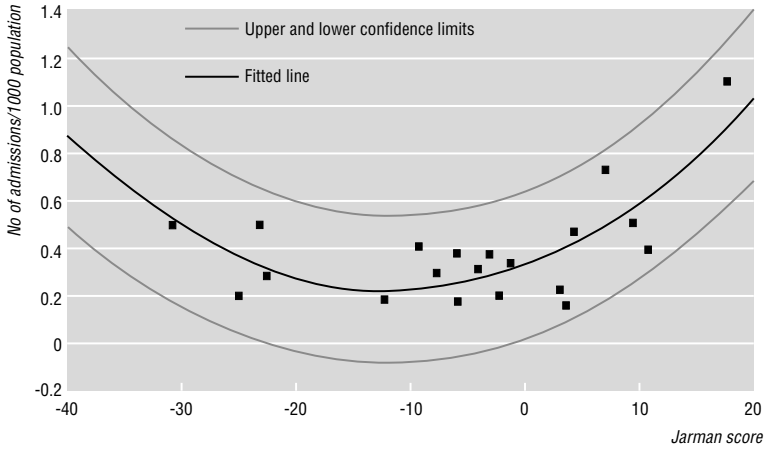

Fig 2 Admissions under Mental Health Act *v* Jarman underprivileged area 8 score (without leverage point)

service, and one had a system of "crisis cards" for discharged patients. Three services provided an intensive support team (defined as being intended for severely mentally ill people; providing evening and weekend cover; having caseloads of less than 20; having the capacity to provide daily visits; and offering long term commitment). None of the services had both a crisis team and an intensive support team.

Bed occupancy levels and social deprivation

Bed occupancy levels for the past 12 months were provided by 26 of the 38 services. These were calculated as the proportion of occupied patient days to number of available beds and included patients who might be on leave, absent without leave, or temporarily transferred to secure facilities (hence occupancy levels could exceed 100%). Figure 1 shows the level for each provider, expressed as a percentage and arranged according to the Jarman score for each provider.

There was a negative relation between the number of available adult acute beds and bed occupancy ($r = -0.51$, 95% confidence interval -0.75 to -0.15, $F = 8.27$, df = 1, 24; $P = 0.008$). There was also a relation between Jarman scores, acute bed availability, and bed occupancy ($r = 0.66$, 0.19 to 0.88, $F = 8.72$, df = 2, 23; $P = 0.002$). The services with low bed availability and high social deprivation therefore appeared to have the highest bed occupancy levels.

When we analysed linear trends with interquartile ranges of Jarman scores, services in more deprived areas had a higher proportion of people with schizophrenia (χ^2 trend = 45.53, df = 1, $P < 0.0001$), people from non-white ethnic groups (χ^2 trend = 9.94, df = 1, $P < 0.01$), and people detained under the Mental Health Act (χ^2 trend = 7.71, df = 1, $P < 0.01$). Overall there was no evidence to suggest a relation between Jarman scores and numbers of admissions (Spearman $r = -0.17$, $P = 0.48$), number of finished consultant episodes ($r = 0.09$, $P = 0.69$), or mean length of finished consultant episodes for past 12 months (Spearman $r = -0.14$, $P = 0.47$). Numbers of admissions under the Mental Health Act per thousand population were related to Jarman scores in a curvilinear (quadratic) relation ($r = 0.97$, 0.90 to 0.99, $F = 163.11$, df = 2, 20; $P < 0.0001$). This held even when one particularly influential point with a high "leverage" value was removed ($r = 0.77$, 0.36 to 0.93, $F = 14.05$, df = 2, 19; $P < 0.0001$). This point simply exerted high leverage and was not actually an outlier. Thus, admissions under the Mental Health Act were higher in the more deprived areas (which were all located in the inner cities), then declined with decreasing deprivation, but increased again in some of the relatively more affluent districts. Figure 2 illustrates these data.

One possible explanation for this very strong statistical relation may be that these districts were all located close to major urban centres (London and Birmingham) and were thus having to cope with an "overspill" from acute beds in the inner cities. Many of these patients were only covered by extracontractual referrals.

Judged needs for admission

In all, 27.2% (603/2215) of current inpatients were judged not to need continuing admission. This proportion was significantly larger (61% (90/148)) among those with stays of more than six months (difference = 36%, 28% to 44%, $\chi^2 = 86.28$, df = 1, $P < 0.0001$). Table 1 shows the reasons preventing discharge in the two groups, excluding those who were on predischarge leave or for whom discharge plans were already in progress. As a check on the validity of these ratings, mean total severity scores on the Health of the Nation outcome scales were calculated for each category for all those patients for whom only one reason was given (91% of total) (table 1).

The most common reason preventing discharge was the non-availability of various community and residential options, in particular the lack of suitable supported housing. A lack of specialised rehabilitation places was seen as a more important reason for the new long stay patients, who were generally much more disabled. The prevalence of these new long stay patients in acute units in general hospitals was higher than in units in mental hospitals. "Requiring higher levels of psychiatric supervision" (which usually meant secure accommodation) contributed to around 10% of the reasons, although this proportion was much higher (17%) among the new long stay patients. "Other" reasons were also important in both categories of

Table 1 Reasons preventing discharge for current admissions of more than or less than six months and Health of the Nation total severity scores* for patients judged to be inappropriately placed

	Stay <6 months (n=482)		Stay >6 months (n=86)		Total severity scores	
Reasons preventing discharge	No of patients	Percentage (SE; 95% confidence interval)	No of patients	Percentage (SE; 95% confidence interval)	No of patients	Mean score (SE; 95% confidence interval)
Lack of housing	176	36.5 (2.5; 31.6 to 41.4)	31	36.0 (4.7; 26.8 to 45.3)	168	10.4 (0.48; 9.5 to 11.4)
Inadequate domiciliary based community support	113	23.4 (2.3; 19.0 to 27.9)	8	9.3 (2.3; 4.7 to 13.9)	88	7.9 (0.64; 6.6 to 9.2)
Lack of rehabilitation places	100	20.7 (1.8; 16.9 to 24.6)	40	46.5 (5.8; 35.2 to 57.8)	107	12.8 (0.70; 11.4 to 14.2)
Requires higher supervision	59	12.2 (2.1; 8.1 to 16.4)	15	17.4 (4.1; 9.4 to 25.5)	48	11.1 (0.93; 9.2 to 13.0)
Other (physically unwell, needs specialist bed, etc)	99	20.5 (2.1; 16.4 to 24.7)	14	16.3 (5.1; 6.4 to 26.2)	100	9.0 (0.63; 7.8 to 10.3)

Percentages do not total 100 owing to multiple responses for some individuals.
*See box in methods section for details.

lengths of stay, and this highlights the shortage of certain specialist placements (for example, for people with acquired brain damage, dual diagnosis of psychosis plus learning disability, drug and alcohol complicated psychosis, and eating disorders). The total severity scores are consistent with the staff judgments, indicating that the most severe problems were among the long term rehabilitation group, followed by those requiring higher levels of supervision, supervised accommodation in the community, and "other" special needs. Patients judged to be able to manage with intensive, domiciliary based support received the lowest total severity scores.

Discussion

These data, collected from a carefully constructed nationally representative sample, support the conclusion that the shortage of beds in acute psychiatric units is related to both social deprivation and lack of available beds. They confirm the unacceptably high levels of bed occupancy (often more than 100%), which are particularly common in inner cities. However, they also suggest that a simple expansion of acute beds would not effectively address the problem.

Over-occupancy is the product of several factors. Firstly, acute beds are "blocked" by patients with relatively short stays who might be more appropriately accommodated elsewhere if suitable intensive community supports were available. Secondly, patients with longer stays need alternative provision of a more specialised and highly supervised kind, which mental hospitals used to provide but which is no longer available. Thirdly, patients with dangerous and violent behaviour need more secure facilities; this is a relatively small group of patients, mainly new long stay patients. Finally, there is a heterogenous group of patients with a range of special needs (for example, patients with acquired brain damage, dual diagnoses, and eating disorders), each subgroup of which are small in number, but who together comprise an appreciable proportion of those misplaced on acute admission wards. They often fall between different specialties (for example, neurology and psychiatry; learning disabilities and general psychiatry) or are simply not numerous enough for a single trust to be able to provide for them. If all the patients who are inappropriately placed on acute admission wards could be relocated then the problem of over-occupancy would be solved. Acute units could then look after only patients whose needs are for immediate treatment and stabilisation of symptoms.

Developing a spectrum of care

To achieve this a spectrum of care must be created, with several residential options for different levels of need and different kinds of problems. Thus, the concept of 24 hour nursed beds may be appropriate for some patients (those requiring longer term intensive rehabilitation in a domestic scale environment) but not for others. Considerable difficulties exist in achieving such a spectrum of care, particularly in the inner cities, with their background of poor housing, high unemployment, and other social problems. Traditionally, long stay patients were transferred out of inner city acute units to the old mental hospitals that ringed the conurbations; the budgets (and services) for mental health services in inner cities therefore never really adequately reflected the need to provide for the most disabled patients.[8] Now that the mental hospitals do not exist or are much smaller, inner cities are struggling to develop specialised (and expensive) services for the most difficult patients, under the least favourable economic and social conditions. Our data also show that these problems are not confined to the inner cities, and there are examples of services in areas with relatively low levels of social deprivation that are in difficulty for precisely the same reasons as those in the inner cities—that is, they have reduced the availability of long term, highly supervised accommodation and have not replaced it with anything else.

These problems cannot be solved without some new resources. However, money will not be enough. Developing good community services means refocusing teams, retraining staff, and reorganising the service to provide access out of hours. At the heart of the service must be various kinds of sheltered and supported housing, and we were therefore concerned that many of our districts could not supply us with accurate information about the range and nature of housing provisions in their area. Similarly, although three quarters of the sample reported having multidisciplinary community mental health teams, we found only three examples of functioning crisis services and the same number of specialist, intensive support teams, specifically focusing on the most severely disabled people, with low caseloads and a commitment to long term care. Without this basic infrastructure, it is difficult to see how mental health services will ever be able to compensate for the loss of mental hospital beds.

Improving effectiveness

The disadvantages of traditional institutional care for long term mentally ill people far outweigh any potential advantages.[14] Most people with long term mental

Key messages

- This study shows that there is a shortage of acute psychiatric beds and that this is related to both social deprivation and the overall availability of beds
- Over a quarter of inpatients were considered to be inappropriately placed on admission wards—for those with lengths of stay of more than six months this figure increased to 61%
- Lack of suitable accommodation, home based support, and rehabilitation places was identified as the major reason preventing discharge
- A range of hospital and community facilities is therefore required to address these problems of over-occupancy and shortages of acute beds

health problems are more satisfied living in the community; they function better; and their care costs no more than it would do in large institutions.[15] The care of patients with severe problems and complex needs may be expensive, but this will be the case wherever they are looked after. Intensive community support, combined with a brief inpatient stay when needed, is also superior to traditional inpatient care and follow up in terms of social outcomes, costs, and patient satisfaction.[16 17] Specialist community teams, if properly resourced and organised, can maintain continuity of care, improve levels of patient satisfaction, and may even produce some clinical and social improvements.[18]

Community care is therefore possible, but all the elements in such a service—including the availability of acute inpatient beds—are interdependent . If community care is to succeed we cannot turn the clock back. We must find a new range of solutions, and this will require both money and ingenuity. We cannot afford to carry on with services and policies that are obviously not working. Neither can we afford to pin our hopes on any single, "magical" solution.

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Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up

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Abstract

Objective: To investigate the contribution of neuroleptic drugs to cognitive decline in dementia.
Design: Two year prospective, longitudinal study consisting of interviews every four months, with necropsy follow up.
Setting: Community settings in Oxfordshire.
Subjects: 71 subjects with dementia, initially living at home with informant.
Main outcome measures: Cognitive function (score from expanded minimental state examination); behavioural problems (physical aggression, hallucinations, persecutory ideas, and disturbance of diurnal rhythm); and postmortem neuropathological assessment (cortical Lewy body pathology).
Results: The mean (SE) decline in cognitive score in the 16 patients who took neuroleptics was twice that in the patients who did not (20.7 (2.9) *v* 9.3 (1.3), $P = 0.002$). An increased rate of decline was also associated with aggression, disturbed diurnal rhythm, and persecutory ideas. However, only use of neuroleptics and severity of persecutory ideas were independently associated with more rapid cognitive decline when all other variables were adjusted for. The start of neuroleptic treatment coincided with more rapid cognitive decline: median rate of decline was 5 (interquartile range 8.5) points per year before treatment and 11 (12) points per year after treatment ($P = 0.02$). Cortical Lewy body pathology did not account for association between neuroleptic use and more rapid decline.
Conclusions: Neuroleptic drugs that are sometimes used to treat behavioural complications of dementia may worsen already poor cognitive function. Randomised controlled trials are needed to confirm a causal relation.

Introduction

Neuroleptic drugs can be of modest benefit in the treatment of behavioural problems in dementia.[1 2] No other class of drugs is of superior efficacy[1]—indeed, only one adequate trial has shown a beneficial effect with a non-neuroleptic drug.[3-5] The frequency of use of neuroleptics has varied widely,[6 7] suggesting that differences in institutional practice contribute substantially to prescribing decisions. In the United States, anxiety about the overuse of neuroleptics in nursing homes has led to federal legislation prohibiting their use for behaviour such as wandering, restlessness, insomnia, or unspecified agitation in the absence of other justifying reasons.[8] A recent survey of nursing homes in Glasgow found that 88% of patients taking neuroleptics might be receiving them inappropriately according to the American guidelines.[9]

The side effects of neuroleptics include the worsening of behavioural disturbance of patients with dementia,[10-12] falls,[13] and fractures.[14] The possibility that the cognitive function of patients with dementia may be made worse by neuroleptics has received little attention. Cross sectional surveys have shown that patients with dementia who take neuroleptics have worse cognitive function than those who do not.[15] However, this might be because neuroleptics are often prescribed for behavioural problems that are more common in patients with severe dementia. Results from studies comparing cognitive function before and after the use of neuroleptics have been conflicting. Some studies have not shown any effect on global assessments,[10 16 17] others have found improvements in memory or orientation,[18-22] and some have shown a worsening of cognitive function.[11 23]

None of these studies examined the long term effects of neuroleptics in dementia or examined the extent to which the effects on cognition were independent of other factors that might affect cognitive function. A more rapid decline in cognitive function has been associated with psychosis,[24-27] hallucinations,[28-31] sleep disturbance, and aggression,[31] but no study has adequately controlled for the possibility that this decline may have been due to the neuroleptics used to treat such behaviours.

Subjects and methods

Subjects

Through general practitioners and community psychiatric nurses, we recruited 104 subjects with dementia (*Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised) who were living at home with carers who were able to give a good account of their symptoms. They were assessed every four months. Six subjects dropped out after two to five interviews and have been excluded from the analyses. Another 27 patients died within 20 months of entry to the study. The remaining 71 patients were assessed on at least six occasions and form the sample for the first multiple regression analysis reported below. Of these 71 patients, 42 underwent postmortem neuropathological assessment and were the sample for the second regression analysis.

Interview

The patients were interviewed every four months and their behaviour assessed with the present behavioural examination.[32] Physical aggression, hallucinations, and persecutory ideas were rated on a seven point frequency scale, relating to the number of days over the four weeks immediately before assessment on which the symptom had occurred. Disturbance of diurnal rhythm that influenced behaviour was rated as present or absent. Non-cognitive symptoms that were clearly related to temporary physical illness were rated as "missing" throughout the study. Cognitive function was assessed with an expanded version of the minimental state examination.[33]

Current medication was recorded at each interview. All doses of neuroleptics were converted to a "chlorpromazine equivalent."[34] In view of the possible adverse effect of low doses in a subgroup of patients[35] we set a low threshold for the definition of substantial neuroleptic use: a mean of 10 mg of chlorpromazine daily over the first 20 months. Our study was conducted before substituted benzamides such as sulpiride were widely used in Britain for treating elderly people. Four drugs accounted for nearly all the neuroleptics prescribed—thioridazine, promazine, haloperidol, and chlorpromazine.

Statistical analysis

The dependent variable in the two multiple regression analyses was the rate of cognitive decline over the first six interviews (that is, the coefficient of regression of minimental state examination score by interview number). In the first analysis, of 71 subjects, the independent variables age, sex, duration of dementia, and cognitive score at study entry were entered simultaneously in a first block. Neuroleptic use and the mean scores over the six interviews for hallucinations, persecutory ideas, physical aggression, and disturbance in

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Table 1 Relation of individual behavioural symptoms to rate of cognitive decline in patients with dementia

Symptom	No (%) of patients with symptom (n=71)	Mean (SE) decline in cognitive function* over 20 months: Symptom present	Symptom absent	Difference
Physical aggression	36 (51)	15.5 (2.0)	8.2 (1.5)	P=0.005
Disturbed diurnal rhythm	26 (37)	17.0 (2.3)	8.9 (1.4)	P=0.004
Persecutory ideas	22 (31)	19.0 (2.6)	8.7 (1.3)	P<0.001
Hallucinations	27 (38)	16.0 (2.4)	9.5 (1.5)	P=0.02

*Measured as score from expanded minimental state examination.

Table 2 Mean (SE) values of possible determinants for use of neuroleptic drugs in 71 patients with dementia

	Neuroleptic treatment*: Yes (n=16)	No (n=55)	Difference (Student's *t* test)
Severity of hallucinations†	0.45 (0.20)	0.42 (0.12)	P=0.9
Severity of persecutory ideas†	0.52 (0.20)	0.30 (0.08)	P=0.3
Severity of physical aggression†	1.36 (0.30)	0.48 (0.12)	P=0.01
Severity of disturbance in diurnal rhythm‡	0.33 (0.86)	0.10 (0.03)	P=0.001
Initial cognitive function§	33.8 (2.85)	32.8 (1.94)	P=0.8
Duration of dementia at study entry (years)	5.8 (1.27)	5.6 (0.47)	P=0.9
Age at study entry (years)	76.6 (1.07)	76.6 (0.92)	P=1.0

*Mean daily dose >10 mg chlorpromazine equivalent over 20 months.
†Mean score over six interviews of rating on seven point scale.
‡Mean score over six interviews of rating on binary scale.
§Measured as score from expanded minimental state examination.

Table 3 Correlation matrix of factors potentially influencing rate of cognitive decline in 71 patients with dementia (values are Pearson *r* coefficients)

	Initial cognitive function†	Duration of dementia at study entry	Age at study entry	Hallucinations‡	Persecutory ideas‡	Aggression‡	Disturbed diurnal rhythm§
Slope of decline in cognitive function¶	–0.05	–0.05	–0.07	–0.27*	–0.41***	–0.37***	–0.36***
Disturbed diurnal rhythm†	–0.14	0.09	0.07	0.37***	0.21	0.39***	
Aggression‡	–0.50***	0.11	0.04	0.29*	0.15		
Persecutory ideas‡	0.05	0.17	0.07	0.31**			
Hallucinations‡	–0.27*	0.03	0.07				
Age at study entry	–0.02	0.23					
Duration of dementia at study entry	0.002						

*P<0.05; **P<0.01; ***P<0.005.
†Measured as score from expanded minimental state examination.
‡Mean score over six interviews of rating on seven point scale.
§Mean score over six interviews of rating on binary scale.
¶Regression coefficient of score of cognitive function at each interview by interview number.

diurnal rhythm were then entered stepwise. We repeated the analysis for the group of 42 patients for whom necropsy data were available, with the addition to the first block of a dichotomous variable indicating the presence or absence of cortical Lewy body pathology.

For the purposes of examining the temporal relation between the start of neuroleptic use and the rate of cognitive decline, we performed a third analysis. We identified 20 patients from the total sample of 98 who were not taking neuroleptics at entry to the study but who started them during the study and continued to take them for at least four months and who had not reached the lowest levels of the expanded minimental state examination when they started taking neuroleptics. We compared the decline in their scores over the year before they started taking neuroleptics with the decline in the year after.

We also compared the 20 subjects' decline in the year after starting neuroleptics with that of 20 matched control patients, drawn from the same sample, who never took neuroleptics. We identified each control on the basis that he or she had the same cognitive score (within four points) as that of the matching subject at the interview immediately before starting neuroleptic treatment. In order to reduce the risk of biased selection of those controls who had a larger number of interviews because they survived longer (a factor which was likely to be associated with a slower rate of cognitive decline), the controls were required to have an equivalent cognitive score at the same point after entry to the study as their matching case. We assessed the significance of these comparisons with unpaired tests (Wilcoxon rank sum) because there were some cases who were not followed for the whole two year period—either because they died within a year of starting neuroleptic treatment or because they started treatment less than a year after entering the study.

Table 4 Results of stepwise multiple linear regression analysis: final model for predicting rate of cognitive decline in patients with dementia

	Regression coefficient B (SE)	P value (df=61)
Sex	0.70 (0.48)	0.15
Age at study entry	–0.04 (0.04)	0.27
Duration of dementia at study entry	0.09 (0.06)	0.15
Initial cognitive function	–0.004 (0.02)	0.82
Severity of persecutory ideas	–1.34 (0.36)	<0.001
Neuroleptic use	–2.05 (0.54)	<0.001

Results

Subjects

Of the 71 patients in our first analysis, 37 were men. The mean (SE) age at entry to the was 72.6 (0.7) years. The age of onset of dementia was less than 65 years in 11 patients, and the mean duration of dementia at study entry was 5.7 (0.5) years. The mean minimental state examination score at study entry was 15.5 (0.9), while the mean score for the expanded version of the examination was 33 (1.6). Of the 42 patients who underwent necropsy, seven had cortical Lewy body pathology and 10 took neuroleptics at some point.

Rate of cognitive decline

The decline in the mean (SE) score for the expanded examination in the patients who took neuroleptics was twice that in those patients who did not (20.7 (2.9) *v* 9.3 (1.3), P = 0.002). An increased rate of decline was also associated with aggression, disturbance of diurnal rhythm, and persecutory ideas (table 1). Furthermore, the patients who were prescribed neuroleptics were more aggressive and had more severe disturbance of diurnal rhythm (table 2). Table 3 shows the extent of correlation between the severity of behavioural changes and other factors that might have predicted a more rapid rate of cognitive decline. There was no correlation between the rate of cognitive decline and the dose of neuroleptic ($r = 0.19$, P = 0.4).

None of the variables that were entered at the first step of the multiple regression analysis (age, sex, duration of dementia, and initial cognitive score), either taken together or separately, made a significant contribution to cognitive decline. Similarly, hallucinations, disturbance of diurnal rhythm, and aggression were excluded from the final model. The final model shows that only neuroleptic treatment and the severity of persecutory ideas were associated with increased rate of cognitive decline once the effect of all the other variables was taken into account (table 4). The significance of these variables as independent predictors was unaffected by square root transformation. The amount of the explained variance in cognitive decline

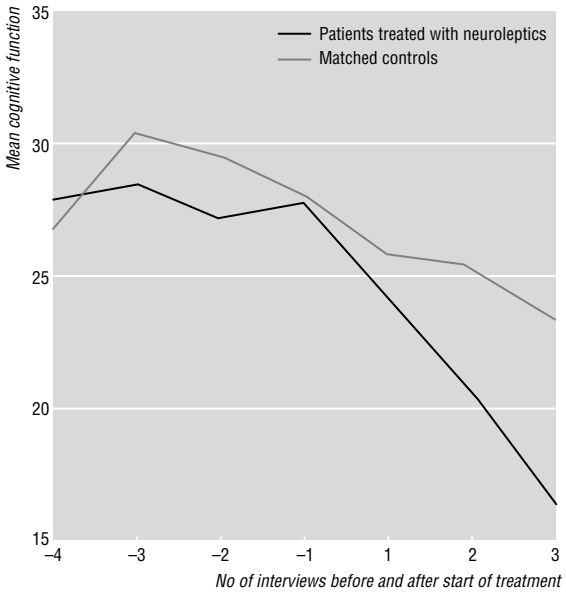

Fig 1 Relation between start of neuroleptic treatment and cognitive function (mean score of expanded minimental state examination) in patients with dementia

that was attributable to the use of neuroleptics was 19.9%.

We repeated the analysis for the 42 subjects who underwent necropsy. Cortical Lewy body pathology did not make an independent contribution to more rapid decline. Neuroleptic treatment remained a significant independent predictor of cognitive decline (data not shown).

Rate of decline before and after taking neuroleptics

Figure 1 shows the pattern of cognitive decline in the 20 patients who started taking neuroleptics after study entry and the pattern of decline in their 20 matched controls. Among the 20 cases, the median (interquartile range) score for cognitive function at the interview before neuroleptic treatment was started was 28.5 (18.5). The median rate of decline in the score over the year before the start of neuroleptic treatment was 5 (8.5) points per year in the 10 cases for whom this information was available. In the 17 cases who were followed for at least a year after neuroleptics were started the median rate of decline was more than twice as fast at 11 (12) points per year. This difference was significant ($W=95$, $z=-2.3$, $P=0.02$). The median decline in scores in the matched controls over the equivalent period was 7.5 (9). This was also significantly lower than the rate of cognitive decline in those taking neuroleptics ($W=377$, $z=-2.3$, $P=0.02$).

Discussion

The main finding in this study was that the use of neuroleptic drugs was associated with an increased rate of cognitive decline in dementia. This association was independent of the degree of dementia and of the behavioural symptoms for which the neuroleptics might have been prescribed. This finding does not, of itself, exclude the possibility that the neuroleptics seemed to cause more rapid decline because patients who were already on a steeper trajectory of cognitive decline were more likely to be prescribed them for reasons other than behavioural problems. However, we also found that the point when patients started treatment with neuroleptics coincided with an increase in their rate of cognitive decline. In addition, we reproduced the findings of others that the rate of cognitive decline is greater in patients who have persecutory ideas.[24 26 27 30]

Robustness of study

One of the main strengths of our study is that it was longitudinal in design and that valid, reliable instruments were used for the collection of behavioural and cognitive data. It was also possible to compare the rates of decline of patients starting neuroleptic treatment over a much longer period than in conventional drug trials. A third advantage was that neuropathological diagnosis was available in over half of our subjects.

Several methodological weaknesses need to be addressed. First, this study is not a randomised controlled trial of the effect of neuroleptics on cognitive decline. Second, subjects' extrapyramidal function was not assessed. The effect of neuroleptics may have been mediated in some way by impaired extrapyramidal function. Third, our sample may have been less homogeneous than others which were confined to patients with clinical Alzheimer's disease. However, most of our subjects had clinical Alzheimer's disease and most of those with clinical vascular dementia also had Alzheimer's disease at autopsy (data not shown), a finding that concurs with that of Galasko *et al.*[36] Fourth, the number of subjects whose cognitive decline was examined before and after starting neuroleptic treatment was small. This militated against the application of statistical tests to multiple time points. The number of statistical tests applied in this analysis was therefore limited by examining only two time points, a year before and a year after the start of treatment, and conventional levels of significance were applied.

Mechanisms for cognitive decline

Our results do not support the idea that the effect of neuroleptics on cognitive function is confined to a subgroup of patients with cortical Lewy body pathology who are particularly sensitive to the drugs.[35] There are several other possible mechanisms by which neuroleptics might contribute to cognitive decline. The most parsimonious explanation is that the anticholinergic effect of the neuroleptics resulted in reduced attention.[12 37] A second possibility is that both the faster cognitive decline and the persecutory ideas were due to unidentified episodes of delirium. Changes in cognitive function might also have been mediated by changes associated with chronic use of neuroleptics, such as enlargement of the caudate nucleus,[38-40] or an increased susceptibility to develop the neurofibrillary change of Alzheimer's disease[41] or impairment of compensatory neurotransmitter responses to neuronal degeneration.[42]

Our results support the hypothesis that neuroleptics contribute to cognitive decline in people with dementia but do not prove it. Randomised controlled

Key messages

- Neuroleptic drugs are used to treat behavioural problems in patients with dementia, but they may cause more rapid decline in cognitive function
- In our longitudinal study of patients with dementia we found that the rate of cognitive decline in patients taking neuroleptics was twice that in those not taking neuroleptics
- Furthermore, the start of neuroleptic treatment was associated with an increase in the rate of cognitive decline
- Cortical Lewy body pathology at necropsy did not account for the association between neuroleptic use and more rapid decline
- Although our study does not prove a causal relation, we suggest that there should be regular review of the need for patients to continue taking neuroleptic drugs

trials are necessary to confirm a causal link. We believe that an appropriate response at present would be to undertake regular review of the need for patients to continue taking neuroleptic drugs, pursuing trials without medication where possible. This study highlights the importance of understanding the neurological basis of behavioural changes in dementia[43] so that less toxic drugs can be developed for their treatment.

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Evaluating the reliability of causes of death in published clinical research

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Deaths during clinical trials or outcome review studies could be due to the disease being studied; adverse complications of interventions in the study; intercurrent disease unrelated to the initial condition or interventions; or unnatural events. Accurate ascertainment of the causes of deaths is therefore required to establish whether treatment has prevented deaths from the investigated disease without concomitant increases in death or morbidity from other causes. We assessed the methods used to evaluate causes of death in published clinical research.

Methods and results

All 879 papers published in 1994 in the *Lancet*, *BMJ*, *Annals of Internal Medicine*, and *New England Journal of Medicine* were reviewed; the methods used to evaluate the causes of death in each paper were recorded using 11 categories (table 1). Death was an outcome measure in 223 papers (25%). The two largest categories of papers were those in which causes of death were either unstated or stated without explanation of the method of ascertainment. The most common stated methods were clinical review committees and registries or databases. Forty two papers (19%) used one or more methods. A necropsy was used in only 29 papers (13%), and the proportion of deaths examined by necropsy varied widely (mean 60%; range 25-100); 15 of these papers failed to include the proportion that underwent necropsy. Four papers were based entirely on necropsy data.

Comment

This survey revealed considerable variation in the methods used to evaluate the causes of death in clinical research. Many publications contained no information about the causes of deaths. Some data may have been omitted through space constraints and editorial processing, but the methods used to ascertain causes of deaths should be stated in all clinical research publications, particularly when so few studies verify more precisely by necropsy the role of interventions in preventing and causing deaths.

Table 1 Methods used to determine causes of deaths in published medical research

Method	No (%) of papers*
Cause of death not stated without explanation	53 (24)
Cause of death stated, method not given	49 (22)
Clinical review committee	34 (15)
Registry or database	34 (15)
Necropsy	29 (13)
Death certificate	24 (11)
Consultation with relatives/consideration of circumstances	14 (6)
Cause of death not stated, with explanation	14 (6)
Cause of death stated, method unclear	13 (6)
Descriptive reports of deaths	11 (5)
Combined data from cohort of separate papers	4 (2)

*42 papers used more than one method thus percentages do not total 100%.

Randomisation is insufficient to permit the assumption that differences between intervention groups in causes of death must be due to the intervention. Although randomisation should ensure that groups are similar, accurate ascertainment of the causes of deaths is still required to establish whether interventions have prevented deaths from the investigated disease without concomitant increases from other causes, including serious adverse events. Apparent disease associated mortality may actually be due to serious complications of treatment; thus a major contribution of a necropsy is the identification of both non-lethal and lethal side effects of medical interventions.[1]

The reasons for low necropsy rates in clinical research are complex and include inability to obtain relatives' consent and difficulties in identifying subjects in clinical trials at the time of death, particularly when it occurs outside hospital. Large multicentre studies may encounter additional problems through local variations in medicolegal practices, necropsy request procedures, and cultural and religious attitudes towards death and necropsy. Although a detailed postmortem examination may not always identify a definitive cause of death, any death which is believed to be related to medical treatment, experimental or otherwise, should be reported to the appropriate medicolegal authority for further investigation. However, medicolegal necropsy data are often unavailable to investigators.

Clinical review committees are commonly used to evaluate causes of death and, when necropsy data are also available, are the most reliable method.[2] Nevertheless, there remains considerable reliance on data from death certificates, which are often inaccurate.[3] Those concerned in performing clinical research should be aware of the limitations of methods used for determining the cause of death. Methods used in individual studies should be clearly stated, and strenuous efforts should be made to include necropsy data. Recent initiatives to improve the reporting of clinical trials are timely,[4 5] and all clinical research in which deaths are expected or represent outcome events should include protocols for evaluating deaths. Ideally, this should be by necropsy in conjunction with clinical information, but we acknowledge that many countries have low necropsy rates and it would not be feasible to make necropsies mandatory.

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